

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (currently amended) An antibody fragment comprising a Fab or Fab' fragment, characterized in that that has been modified by replacement of either the interchain cysteine of C_H1 or the interchain cysteine of C_L has been replaced by with another amino acid.
2. (currently amended) The antibody Fab' fragment of ~~claim 1~~ claim 44 ~~that contains~~ comprising a modified hinge region.
3. (currently amended) The antibody Fab' fragment of claim 2 ~~in which~~ wherein the hinge region comprises ~~or consists of~~ any one of the sequences provided in SEQ ID Nos 1-14.
4. (currently amended) The antibody Fab' fragment of claim 2 ~~and claim 3 in which~~ wherein the C_L interchain cysteine is covalently bonded to a cysteine in the hinge region.
5. (currently amended) An antibody Fab' fragment, ~~characterized in that~~ in which both the interchain cysteine of C_H1 and the interchain cysteine of C_L have been replaced by another amino acid and an engineered cysteine in the light chain constant region is covalently bonded to a cysteine in the hinge region.
6. (currently amended) The antibody Fab' fragment of claim 5 ~~in which~~ wherein the light chain constant region comprises ~~or consists of~~ any one of the sequences provided in SEQ ID Nos 16-20.
7. (currently amended) The antibody Fab' fragment of claim 6 ~~in which~~ wherein the hinge region comprises ~~or consists of~~ any one of the sequences provided in SEQ ID Nos 1-11.

8. (currently amended) ~~An~~ The antibody Fab² fragment, ~~characterized in that~~ of claim 1 wherein the fragment is a Fab' fragment in which the interchain cysteine of C_L has been replaced by another amino acid.
9. (currently amended) The antibody Fab² fragment of claim 8 ~~that~~ wherein the fragment contains a modified hinge region.
10. (currently amended) ~~An~~ The antibody Fab fragment, ~~characterized in that~~ of claim 1 wherein the fragment is a Fab fragment in which the C_{H1} interchain cysteine has been replaced by another amino acid.
11. (currently amended) ~~An~~ The antibody Fab fragment, ~~characterized in that~~ of claim 1 wherein the fragment is a Fab fragment in which the C_L interchain cysteine has been replaced by another amino acid.
12. (currently amended) The antibody ~~Fab or Fab²~~ fragment of ~~claims 1 to 11~~ claim 1 ~~where~~ wherein the interchain cysteine that has been replaced has been replaced by a non-thiol containing amino acid.
13. (currently amended) The antibody ~~Fab or Fab²~~ fragment of claim 12 wherein the non-thiol containing amino acid is serine.
14. (currently amended) The antibody ~~Fab or Fab²~~ fragment of ~~claims 1 to 13 to which~~ claim 1 wherein at least two effector molecules are attached to the fragment.
15. (currently amended) The antibody ~~Fab or Fab²~~ fragment of claim 14 ~~where~~ wherein an effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region.
16. (currently amended) The antibody fragment of claim 15, wherein an effector molecule is attached to a cysteine in the light chain constant region and to a cysteine in the

heavy chain constant region, ~~which~~ wherein the two cysteines would otherwise be linked to each other via a disulphide bond if the effector molecules were not attached.

17. (currently amended) The antibody fragment of ~~claims 14-16 where~~ claim 14 wherein an effector molecule is attached to the interchain cysteine of C_{L2} ~~or to~~ to the interchain cysteine of C_{H12}, or to an engineered cysteine in the light chain constant region, ~~whichever is present in the fragment.~~

18. (currently amended) ~~An~~ The antibody Fab² fragment ~~according to claims 14-17 where~~ of claim 1 wherein the fragment is a Fab' fragment in which an effector molecule is attached to each cysteine in the hinge region.

19. (currently amended) ~~An~~ The antibody Fab² fragment ~~according to~~ of claim 18 ~~where~~ wherein an effector molecule is attached to a cysteine in the hinge ~~which~~ region that was covalently linked to the interchain cysteine of C_L prior to attachment of the effector molecules.

20. (currently amended) ~~An~~ The antibody Fab² fragment ~~according to~~ of claim 18 ~~where~~ wherein an effector molecule is attached to a cysteine in the hinge ~~which~~ region that was covalently linked to an engineered cysteine in the light chain constant region prior to attachment of the effector molecules.

21. (currently amended) A method of producing an antibody ~~Fab or Fab'~~ fragment ~~according to claims 14-20~~ of claim 14 comprising:

- a. ~~Treating~~ treating an antibody ~~Fab or Fab'~~ fragment ~~according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13~~ an antibody Fab or Fab' fragment in which either the interchain cysteine of C_{H1} or the interchain cysteine of C_L has been replaced by another amino acid with a reducing agent capable of generating a free thiol group in at least one cysteine of the heavy and/or light chain constant region and/or, where present, the hinge; and
- b. ~~Reacting~~ reacting the treated fragment with an effector molecule.

22. (currently amended) The method of claim 21 ~~where~~ wherein step (a) further comprises ~~where present~~, reducing the covalent bond between the C_L interchain cysteine and a cysteine in the hinge region.

23. (currently amended) The method of claim 21 ~~where~~ wherein step (a) further comprises ~~where present~~, reducing the covalent bond between an engineered cysteine in the light chain constant region and a cysteine in the hinge region.

24. (currently amended) An antibody fragment comprising a Fab or Fab' fragment ~~to which~~ that has been modified by attachment of two or more effector molecules ~~are attached~~ characterised in that wherein the heavy chain in the fragment is not covalently bonded to the light chain, and an effector molecule is attached to each of the interchain cysteines of C_L and C_{H1}.

25. (currently amended) The antibody ~~Fab or Fab'~~ fragment of claim 24 ~~where~~ wherein at least one further effector molecule is attached to a cysteine in the light chain constant region and/or to a cysteine in the heavy chain constant region.

26. (currently amended) The antibody fragment of claim 25, wherein an effector molecule is attached to a cysteine in the light chain constant region and to a cysteine in the heavy chain constant region, ~~which~~ and the two cysteines would otherwise be linked to each other via a disulphide bond if the effector molecules were not attached.

27. (currently amended) ~~An~~ The antibody ~~Fab'~~ fragment ~~according to~~ of claim 26 wherein the fragment is a Fab' fragment that contains a modified hinge region.

28. (currently amended) The antibody ~~Fab'~~ fragment of claim 27 ~~in which~~ wherein the hinge region comprises ~~or consists of~~ any one of the sequences provided in SEQ ID Nos 1-14.

29. (currently amended) ~~An~~ The antibody Fab² fragment ~~according to claims 24-28 of claim 24 wherein the fragment is a Fab' fragment and~~ an effector molecule is attached to at least one cysteine in the hinge region.

30. (currently amended) A method of producing an antibody ~~Fab or Fab'~~ fragment ~~according to claims 24-29 of claim 24~~ comprising:

- a. ~~Treating~~ treating an antibody Fab or Fab' fragment with a reducing agent capable of generating a free thiol group in at least the interchain cysteine of C_{H1} and the interchain cysteine of C_L; and
- b. ~~Reacting~~ reacting the treated fragment with an effector molecule.

31. (currently amended) The antibody ~~fragments~~ fragment of ~~claims 1-30 where~~ claims 1 or 24 wherein the interchain cysteine of C_L is at position 214 of the light chain and the interchain cysteine of C_{H1} is at position 233 of the heavy chain.

32. (currently amended) The method ~~according to~~ of claims 21 ~~and or~~ 30 ~~in which~~ wherein the reducing agent is a non-thiol based ~~reductant~~ reducing agent.

33. (currently amended) The method ~~according to~~ of claim 32 ~~in which~~ wherein the ~~reductant~~ reducing agent is a trialkylphosphine.

34. (currently amended) The method ~~according to~~ of claim 33 ~~in which~~ wherein the trialkylphosphine ~~reductant~~ reducing agent is tris(2-carboxyethyl)phosphine (TCEP).

35. (currently amended) The method ~~according to~~ of claim 33 ~~in which~~ wherein the trialkylphosphine ~~reductant~~ reducing agent is tris(3-hydroxypropyl)phosphine (THP).

36. (currently amended) The method ~~according to~~ of ~~claims 21 and 30~~ claim 21 ~~in which~~ wherein either or both of steps (a) and (b) are performed in the presence of a chelating agent.

37. (currently amended) The method ~~according to~~ of claim 36 ~~in which~~ wherein the chelating agent is EDTA.
38. (currently amended) The method ~~according to~~ of claim 37 ~~in which~~ wherein both steps (a) and (b) are performed in the presence of EDTA.
39. (currently amended) A ~~mixture composition containing~~ comprising a mixture of two or more antibody Fab or Fab' fragments, ~~characterized in that~~ wherein the mixture is enriched for Fab or Fab' fragments in which the heavy chains in the fragments are not covalently bonded to the light chains, the fragments have two or more effector molecules attached, and at least one of said effector molecules is attached to a cysteine in the light chain or the heavy chain constant region of the fragments.
40. (currently amended) The ~~mixture composition~~ of claim 39 ~~in which~~ wherein greater than 50% of the mixture comprises a Fab' or Fab ~~fragment~~ fragments in which the heavy ~~chain chains~~ in the fragment is fragments are not covalently bonded to the light ~~chain chains~~, the ~~fragment has~~ fragments have two or more effector molecules attached, and at least one of said effector molecules is attached to a cysteine in the light chain or the heavy chain constant region of the fragments.
41. (currently amended) The antibody fragment of ~~claims 14 31 and 39 40~~ claims 14 or 24 wherein the effector molecule is PEG.
42. (currently amended) A host cell expressing the antibody fragment of ~~claims 1 13~~ claim 1.
43. (currently amended) A pharmaceutical composition comprising an antibody fragment ~~according to any of the preceding claims~~ of claims 1 or 24, together with one or more pharmaceutically acceptable excipients, diluents or carriers.
44. (new) The antibody fragment of claim 1 wherein the fragment is a Fab' fragment in which the interchain cysteine of C_H1 has been replaced by another amino acid.